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BRONCHIAL COMPLICATIONS AFTER LUNG TRANSPLANTATION

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Bronchial complications are among the main causes of impairing postoperative period and thansplant failure. Severe bronchial complications are very rare but have a high mortality rate. Light forms decrease transplant function and while progressing can leads to life-threatening conditions without required treatment. Nowadays there is a huge necessity in classification of diagnostic and bronchial complications treatment on different terms after lung transplantation. Methods of observation bronchoscopy and interventional bronchology are allowing us to realize prevention, diagnostic and treatment bronchial complications.

Keywords: lung transplantation, bronchial arteries, anastomotic dehiscence, bronchial stenosis, bronchomalacia, bronchial stenting, interventional bronchology.

The development and evolution history of approaches to the treating bronchial complications in donor lung recipients has been quite dramatic. The first lung graft was made by J.D. Hardy et al., in 1963 in a 58-year-old patient with central left lung cancer. The patient's condition was complicated by obstructive pneumonia resulted from tumor occlusion of the left main bronchus, emphysema of the lungs and chronic glomerulonephritis. Considering the respiratory failure events against the background of expressed emphysematous changes, the only possible method of treatment was an attempt to transplant the left lung.

On June 11, 1963, a one-lung graft from a cadaver donor was performed. The immunosuppression protocol included azothioprine, prednisone and mediastinal irradiation. The course of the postoperative period was complicated by the failure of the bronchial anastomosis, which required continuous active aspiration from the left pleural cavity. The patient died on the 18th day after transplantation of infectious complications and renal failure. Autopsy of the left pleural cavity revealed limited empyema and bronchial anastomotic dehiscence in the area of the membranous wall of up to 5 millimeters long [1].

In 1971, C. Bernard et al. performed the third in history transplantation of the cardiopulmonary complex. The patient died on the 23rd day of sepsis against the background of pleural empyema developed as a result of tracheal anastomosis leak [2].

In 1978, J.D. Cooper et al. performed the first of the transplant under extracorporeal membrane oxygenation. The patient died on the 18th day. Autopsy revealed circular necrosis of the graft bronchus of up to 2 cm long [3].

The period from 1963 to 1978 was featured by sporadic reports of transplants performed. Of 38 observations, only 9 patients survived for over 2 weeks after surgery, and only one patient was discharged from the clinic. In the overwhelming majority of cases, adverse outcomes were caused by the failure of the bronchial or tracheal anastomoses [4].

A number of scientific studies and experiments revealed the negative effect of azathioprine and high doses of glucocorticoids on the repair processes in the area of bronchial anastomosis [5]. The introduction of Cyclosporin A (Sandoz Pharmaceutical Company) into clinical practice has significantly improved the immediate outcomes of LT, such as by reducing the rate of bronchial anastomoses leakage [6]. Epiplopexy of bronchial anastomosis and the use of other plastic materials (intercostal muscles, pericardium) to cover it and enhance neoangiogenesis were also proposed as a possible solution to the problem [7]. Revascularization of the bronchial arteries of a pulmonary graft has significantly reduced the incidence of early bronchial complications, but to date this method has not become widespread due to its technical complexity [8].

A lower incidence of bronchial complications during transplantation of the cardiopulmonary complex was established when compared to isolated lung transplantation. That can be explained not only by the preservation of blood supply through the bronchial arteries, but also by the reduction in the time of pulmonary ischemia in the composition of the cardiopulmonary transplant. On the basis of these regularities, the domino transplant was taken as a solution to the problem of bronchial anastomotic dehiscence. The technique consisted in transplanting the cardiopulmonary complex to a patient in need of isolated

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LT, while the heart of the first recipient, under safety conditions, was transplanted to patient No. 2 [9, 10].

Bilateral en-block lung transplantation with the tracheal anastomosis formation was accompanied by an unacceptably high leakage rate, which was the reason for the technique to be widely rejected[11].

Progress in surgical technique, preservation of donor organs, approaches to drug immunosuppression significantly improved both immediate and long-term outcomes of lung transplantation, which made it possible to reduce the rate of bronchial complications from 60–80% in the first year after surgery to 2–18%, while lowering mortality to 2–4% [12–14]. Nevertheless, bronchial complications in donor recipients remain one of the main reasons for the development of adverse outcomes at different times after lung transplantation.

ETIOLOGY OF BRONCHIAL COMPLICATIONS

The bronchial tree is known to receive blood supply through the bronchial arteries starting from the aorta or intercostal arteries and, to a lesser extent, collateral blood supply at the level of the submucosa from the bed of the pulmonary artery. One of the main reasons for the development of bronchial complications (BCs) both in the early postoperative period and in the long term after transplantation is the bronchial arteries transection at the graft removal. The current, generally accepted surgical technique does not imply their routine reconstruction, as a result of which the blood supply to the tissues of the respiratory tract continues to be carried out only by venous blood from the bed of the pulmonary artery through the collaterals of the submucosal layer, which leads to the development of ischemia and dystrophic processes, both in the area of the anastomosis and throughout the bronchial tree. Revascularization of the bronchial arteries of a pulmonary graft can be considered as a method of BC prevention in the early postoperative period [15], but the role of this technique in the prevention of late BC has not been reliably confirmed [16].

The maximum shortening of the stump of the main bronchus of the graft to 1–2 cartilaginous semi-rings from the upper lobe bronchus spur was found to reduce the rate of bronchial anastomosis leakage from 11.1% to 2.6%. In addition, the importance of smooth dissection of the graft root area and minimal skeletonization of the bronchial stump to preserve lymphoid, pericardial tissue and tissue used as plastic material for covering the suture line, preserving microcirculation, and collateral blood supply to tissues in the area of bronchial anastomosis has been proven [17].

Effective collateral blood supply to the bronchial tree of the graft is restored within 2–4 weeks [8]. A number of factors have been established that affect these processes, and therefore are capable of aggravating the phenomena of ischemia and the risks of developing bronchial complications. These factors include:

- Donor lung conservation technique.
- Ischemic-reperfusion injury of a lung graft.
- Primary lung graft dysfunction.
- Graft rejection.
- Infectious and inflammatory changes.
- Prolonged mechanical ventilation with high PEEP values.

It has been proven that the donor lungs preservation in dextran solutions with low Ca concentration (at the rate of 60 ml/kg) with the addition of prostaglandin E to the perfusate, during ante- and retrograde perfusion, allows not only to prolong the length of safe storage (conservation) of donor organs to 12–14 hours and according to some reports and in the experiment, up to 22–25 hours, but also to reduce the BC rate [18].

On the other hand, there are conflicting opinions on the absence of significant differences in the BC rates depending on the duration of ischemia of a pulmonary graft [19], as well as about the greater likelihood of developing BC from the side of the graft implanted in the second place in two-lung transplantation [20].

Ischemic attacks, inflammatory changes and acute rejection events lead to edema of the mucous and submucous layer of the respiratory tract, entailing an increase in vascular resistance at the microcirculatory level. Ischemic attacks can increase, resulting from the reduction in pulmonary blood flow against a background of hypotension, a decrease in cardiac output and the use of vasopressors [21].

Primary dysfunction of the lung graft expressed as an interstitial edema, damage to the alveolar-capillary barrier, shunting and reduction of pulmonary blood flow, aggravates ischemia of bronchial tissues. Primary dysfunction necessitates prolonged mechanical ventilation, often severe (high PEEP), which creates additional risks of BC development [22].

Acute rejection events lead to damage to the alveolar epithelium, vascular endothelium, which subsequently increases the risk of developing bronchial stenosis during the first year after transplantation [23].

At the early stages of the lung transplantation development, there was a generally accepted belief in the negative effect of high doses of corticosteroids on the repair processes in the area of the bronchial anastomosis, and the use of corticosteroids before transplantation was considered as contraindications to surgery [24]. To date, the opinion of the majority of researchers is represented by diametrically opposite views, noting positive effects in the form of a decrease in the rate and intensity of the formation of endobronchial granulation tissue and decreased risk of developing rejection [12, 25].

The effects of proliferative signal inhibitors (Everolimus) expressed in endothelial, smooth muscle cells

and fibroblasts have been proven to reduce the frequency and rate of progression of chronic rejection in the form of bronchiolitis obliterans syndrome. The same effects underlie the principles of combined treatment of bronchial stenosis by a combination of endoscopic bronchoplasty methods and long Everolimus administration. On the other hand, antiproliferative effects can lead to such disastrous consequences as the development of bronchial anastomotic dehiscence at the early stages after transplantation. This makes it possible to administer a four-component immunosuppression no earlier than 3 months after transplantation [26].

Along with ischemia, respiratory tract infection plays an important role in the development of bronchial complications. Necrotic changes in the mucous membrane of the bronchial tree both in the area of the anastomosis and throughout, drug immunosuppression, direct contact of the transplanted organ with the environment, lack of effective ciliary clearance, cough reflex weakening – all these create favorable conditions for infection persistence in the respiratory tract. In this context, of particular importance is a fungal infection that develops with a rate of 15–35% and is represented by *Aspergillus* and *Candida* fungi in 80% of cases [27]. The most aggressive type of fungal infection, *Aspergillus* fungi, is expressed in the form of pseudomembranous or necrotic *Aspergillus*-associated tracheobronchitis and invasive pulmonary aspergillosis. Mortality in the development of generalized fungal infection, especially in the case of invasive forms, reaches 100% [28].

Some studies proved that chronic infection with highly virulent multi-resistant gram-negative microflora (*P. aeruginosa, B. cepacia*) increases the rate of bronchial complications by 29% [29].

Drug-induced immunosuppression is a risk factor for opportunistic infections (*P. carinii; Aspergillosis*, CMV). The likelihood of developing pneumocystis pneumonia in patients not receiving appropriate antimicrobial therapy is more than 80% [30]. The devastating consequences of infection and the development of opportunistic infections are considered in the standard regimen of antimicrobial prophylaxis in lung recipients.

It was found that long mechanical ventilation (50–70 h or longer) and high PEEP values result in damage to the bronchial mucosa and bronchial wall in the anastomotic area and are also associated with high risks of infectious complications [17, 29].

It is argued that performing a "telescopic" bronchial anastomosis in 48% of cases is complicated by development of bronchial stenoses, while the end-to-end anastomosis provides a lower rate of such complications and is thus more preferable [16].

Suture technique is equally important. The generally accepted technique is a combined bronchial anastomosis with the formation of a continuous twisted suture of the membranous part of the bronchus and a single interrupted suture of the cartilaginous part of the bronchus. For effective comparison of cartilaginous half-rings, some authors recommend performing 8-shaped sutures, which allows minimizing the number of probable bronchial anastomosis complications from 18.1 to 2.3% [13].

Despite the lengthy discussions on the benefits of a particular surgical technique and the option of bronchial anastomosis, a consensus has not yet been reached, and the choice is determined by the immediate operation conditions and the surgeon's own experience and preferences. In some cases, performing a bronchial telescopic anastomosis is necessary to compensate for the difference in the diameter of the bronchus of the donor and recipient.

CLASSIFICATION OF BRONCHIAL COMPLICATIONS

Bronchial anastomotic dehiscence

Ischemic disorders in the bronchial tissues of the graft lead to desquamation of the bronchial epithelium and the development of anastomosis of varying severity. The most severe form is necrotic anastomosis's, a condition that potentially threatens the development of bronchial anastomosis failure.

The bronchial anastomotic dehiscence (BAD) is a violation of the integrity and tightness of the suture of the bronchial anastomosis as a result of necrotic changes extending to the entire thickness of the wall of the bronchial stump of the graft, leading to the formation of both length-limited defects and complete anastomosis separation. It develops with a rate of 1 to 10% within 1 to 4 weeks after transplantation and is features with a high mortality rate [12]. The clinical picture differs depending on the degree and extent of the dehiscence.

In some cases, dehiscence is latent, without clear clinical manifestations and is diagnosed during routine bronchoscopy. CT of the chest organs is a highly sensitive method for diagnosing BAD, as it allows both to directly visualize a defect in the bronchial wall and to identify it by indirect signs in the form of a limited peribronchial air accumulation.

The development of a necrotic anastomosis is not an absolute predictor of BAD development; however, it makes it mandatory to conduct regular observational and sanitary bronchoscopy to monitor changes.

In itself, the fact of revealing the bronchial anastomosis dehiscence is not an indication for emergency surgery. The tactics are determined by the length of the defect, the clinical picture and the effectiveness of conservative therapy. With defects of less than 25% of the anastomosis circumference, in the absence of clinical manifestations, waiting is preferred; if a defect is larger than 25% of the circumference, or if symptoms are present, interventional

bronchoscopic or surgical reconstructive interventions are performed [31].

In case the dehiscence of a limited length is developed, self-expanding metal stent implantation is recommended. The choice of the stent option is a subject for discussion; however, most authors are inclined to the implantation of uncoated nitinol stents that do not interfere with neoepithelialization for 6 to 8 weeks [12, 32]. Coated stents prevent effective ciliary clearance of the airway mucosa, creating favorable conditions for infectious colonization of the anastomotic region [33, 34]. The limitation of the time of implantation is due to the risk of granulation tissue growing on an uncoated stent up to its complete occlusion, which significantly complicates its subsequent removal, potentially threatening the formation of a secondary defect that is even larger than the initial one [32, 33].

Some observations on effective therapy of short-length bronchial anastomosis leakage by instillation of surgical glue based on fibrin or cyanoacryalate on the defect area have been published [35, 36]. In case of ineffectiveness of conservative and minimally invasive methods of treatment, attempts are made to close the defect with additional covering of the suture line with the recipient's own tissues with preserved blood circulation (intercostal muscles, pericardium, strand of the greater omentum on the feeding pedicle), and reconstructive bronchoplastic operations are performed. If reconstruction is impossible or in case of development of repeated failure, if the patient's condition allows, transplantatectomy is performed.

Bronchial fistulas

Bronchial fistula is a pathological fistulous communication of the bronchus lumen with anatomically similar structures or cavities, depending on which they are subdivided into bronchopleural, bronchomediastinal and bronchovascular.

Bronchopleural fistulas develop in the early postoperative period and are typically associated with 12% of cases of bronchial anastomoses dehiscence [36]. The clinical picture is featured with the development of pneumothorax, which persists for a long time despite constant active aspiration from the pleural cavity, and subcutaneous emphysema. The presence of a direct communication of the pleural cavity with the bronchus lumen leads to development of pleural empyema, resulting in sepsis. Diagnostic and therapeutic tactics are identical to the corresponding approaches in the case of bronchial anastomosis dehiscence, and the same for bronchomediastinal fistulas [36, 37].

Bronchovascular fistula is a rare complication described in isolated cases [38]. First, it is associated with BA dehiscence against the background of persistent bronchial, most often fungal infection (*Aspergillus, Candida*). In the published observations, the development of bronchovascular fistulas involved the aorta, pulmonary arteries, azygos vein, and left atrium. The formation of a bronchovascular fistula leads to the development of arrosive, often fatal, pulmonary hemorrhage. The development of air embolism has been described in [39] A few publications show cases of rescuing a patient with transplantatectomy or resection of a lung graft of various sizes [40].

Bronchial anastomosis dehiscence and bronchial fistulas in terms of the time of their occurrence are early bronchial complications that develop in up to 3 months after lung transplantation. For periods of more than three months, the following bronchial complications are characteristic:

– Bronchial stenosis.
– Endobronchial hypergranulation.
– Bronchomalacia.

Bronchial stenosis

Bronchial stenosis (BS) is a fixed, breathing act-independent, persistent narrowing of the diameter of the bronchi lumen developing mainly as a result of cicatricial changes with a rate of 1.6–32%. BS can develop at any time after LT but is most often during the first 2 to 9 months after transplantation. Depending on the localization relative to the bronchial anastomosis, they are classified into central and peripheral. The central stenoses are localized directly in the area of the anastomosis or near, but no further than 2 cm. According to various estimates, they are observed in 12–40% of cases. Distal bronchial stenoses are localized more than 2 cm from the bronchial anastomosis and are recorded in 2.5–3% of recipients [41]. The most severe form of peripheral bronchial stenosis is the syndrome of the disappearing intermediate bronchus, which develops with a frequency of about 2%. It has been established that the median survival rate of recipients of donor lungs after the diagnosis of disappearing intermediate bronchus syndrome is about 25 months [42].

The clinical picture is shortness of breath, cough, rales, and the development of obstructive pneumonia in the extreme form. Respiratory function examination shows obstructive breathing patterns. Depending on the degree of stenosis, the condition may be asymptomatic. In some cases, up to 50% of the obstruction of the bronchus lumen can be found accidentally at diagnostic bronchoscopy. Diagnosis is based on characteristic endoscopic and CT images.

Treatment is consistent. The first-line therapy includes methods of interventional bronchology with increasing degree of invasiveness: balloon dilatation, electro- and argon-plasma coagulation, cryotherapy, and implantation of bronchial stents. These techniques are used both independently and in combination.

Balloon dilation (balloon bronchoplasty) is especially preferred if obstructive pneumonia develops as a result of cicatricial stenosis. In 26% of cases, thanks to balloon bronchoplasty, it is possible to achieve stable outcomes without the need for stent implantation in the future. In other cases, at least 2 attempts to dilate bronchial stenosis are recommended before deciding on the bronchial stent implantation [37].

If restenosis develops after repeated balloon bronchoplasty attempts, bronchial stent implantation is indicated [43].

The choice of the type of stent remains a subject for discussion and a specific clinical situation. The main advantage of silicone stents (SS) (Dumont type) is their easy removal even after long periods of implantation. The disadvantage is that a rigid bronchoscopy is needed for its installation.

A metal stent, despite the convenience of implantation, in particular the possibility of implantation through the working channel of a video bronchoscope, has limited indications for use due to the risk of germination by granulation tissue, which limits the time of safe use to 3–4 weeks, otherwise leading to mechanical damage when trying to remove it.

Combined (hybrid) stents of nitinol (an alloy of titanium and nickel), coated with a polymer shell, having all the benefits of metal (ease of implantation) and silicone stents (ease and atraumatic removal), are currently an option of choice. A promising trend in bronchial stenosis treatment is the use of biodegradable and drug-eluting stents [44]. Despite the long existence of bronchial stenting as a therapeutic option for lung transplantation, to date, the advantage of certain stents within the framework of the tasks considered has not been established in randomized trials.

Incorrect stent selection and long implantation periods are accompanied by the development of complications in 50% of cases. Most often, stent migration, parietal and borderline proliferation of tissue granulations, and in the case of uncoated stents and their germination up to complete occlusion, obturation of the lumen with thick bronchial discharge occur [45].

The recommended duration of implantation of a silicone or combined stent is 6–8 months on average; then it is possible to completely resolve cicatricial stenosis as a result of bronchial remodeling. Separate observations show the period of safe implantation of bronchial stents of up to 7 years [46]. It has been established that the median survival rate of patients after bronchial stenting is 82 months versus 22 in patients after isolated balloon bronchoplasty [47].

Endobronchial hypergranulation

The development of endobronchial hypergranulation (EH) is accompanied with impaired ventilation risk due to the risk of airway obstruction. Hyperplastic granulation growths are typically formed in the area of bronchial anastomosis within 3–4 months after lung transplantation, which, according to various estimates, in 7–24% of cases leads to the development of clinically significant obstruction. The growth of granulation tissue is also provoked by trauma to the mucous membrane of the respiratory tract during endoscopic manipulations, laser coagulation, electrosurgical manipulations, and placement of bronchial stents. Infection with fungal flora in the area of bronchial anastomosis is a recognized risk factor for excessive development of granulation tissue [21, 48].

The approaches to endobronchial hypergranulation treatment are controversial. The decisive factor to choose the particular tactics is the degree of obstruction. Waiting tactics are recommended when areas of granulation are detected that cover up to 25% of the bronchial lumen and in the absence of a clinical picture. The question naturally arises about the expediency of waiting since lack of treatment will inevitably lead to continued growth of granulation tissue. In the case of obstruction of the lumen of the bronchus by more than 25% or in the presence of productive symptoms, their removal is indicated [31].

Endobronchial hypergranulations are treated by interventional bronchology techniques. Mechanical removal of granulation tissue with biopsy forceps during flexible endoscopy has advantages in comparison with electrosurgical methods of treatment, when using which excessive trauma to the bronchial wall can lead to inflammatory changes and provoke further growth of granulation tissue. A promising direction in the therapy of hypergranulations is cryotherapy in combination with mechanical removal of frozen tissues, which is accompanied by a lower frequency of relapses. Despite the variety of treatment methods, the repeated development of endobronchial hypergranulations, according to various sources, takes place in 10–50% of cases [12, 14, 37].

Given the high recurrence rate of cicatricial stenosis and endobronchial granulations, new methods and therapeutic approaches are proposed. Brachytherapy [49] and photodynamic therapy [50] are suggested as possible treatment options. A promising direction is the local use of antitumor, antiproliferative agents. Mitomycin C inhibits fibroblast proliferation and is used as a short-term application of a tampon with a solution (concentration 0.1–1 mg/ml, 0.4 mg/ml on average) for 2 to 5 minutes to the bronchial wall area after removal of granulation tissue or to the area of cicatricial stenosis [51].

There is evidence of the effectiveness of a combination of interventional bronchology methods with the appointment of proliferative signal inhibitors (m-TOR inhibitors), but this issue needs further study [52].

In the absence of the effect of the considered conservative, minimally invasive techniques and their combinations in the treatment of bronchial stenosis, recons-

tructive and bronchoplastic surgical interventions, to resection of a lung transplant in various volumes are forced [53, 54].

Bronchomalacia

Bronchomalacia (BM), or expiratory collapse of the airways, is a condition in which exhalation is accompanied by a decrease in the diameter of the bronchial lumen by more than 50% as a result of the loss of the supporting function by the cartilaginous framework of the bronchi, hypotension of myoelastic elements. It is localized mainly in the area of bronchial anastomosis and distal airways [12, 14, 37], which, depending on the severity, can lead to violation of the ventilation conditions.

The development of bronchomalacia is observed in 1–4% of cases within 4 months after LT. The etiology is poorly understood, it is assumed that BM is associated with ischemic damage, persistent infection, and immunosuppression regimens. It is classified depending on the localization into peribronchial (within 1 cm from the anastomotic line) and distal BM [12, 37].

The clinical picture is shortness of breath, more in the supine position, the participation of auxiliary muscles in the act of breathing, difficult expectoration, recurrent infectious attacks, and a chronic barking cough.

Instrumental diagnostics includes the assessment of dynamic expiratory changes in the diameter of the bronchi at chest CT or bronchoscopy [37].

Modern approaches to the therapy of bronchomalacia aimed at reducing the severity of symptoms of the disease and improving the quality of life include conservative approaches, minimally invasive endoscopic methods and methods of surgical correction. In the absence of symptoms, when bronchomalacia is an accidental diagnostic finding, therapy is not indicated. As a conservative method of treatment, non-invasive ventilation of the lungs is used, which prevents the development of collapse of the airways due to the positive end-expiratory pressure. This method is the initial stage in the treatment of bronchomalacia, aimed at reducing shortness of breath, paroxysmal cough, improving sputum discharge, which makes it possible to compensate for the severity of symptoms and is carried out mainly at night or on demand. In case of severity of symptoms, frequent infectious exacerbations, constant dependence on noninvasive ventilatory support, stent implantation is performed. The choice in this case is the Dumont or combined nitinol stent. The stent creates a rigid framework that prevents the expiratory collapse of the airway, reducing the manifestation of symptoms, and improving the patient's quality of life. When the malacia area is localized at the level of the main bronchi, it becomes necessary to use Y- or J-shaped stents, the effective fixation of which in the airway lumen is achieved due to the tracheal segment of the stent. The placement of the stent is carried out with the expectation of remodeling of the bronchus, which is assessed after its removal within 6–8 months. According to some authors, the optimal duration of silicone stent implantation is 9–12 months [47]. In the absence of remodeling of the bronchomalacia region, they are forced to resort to repeated stenting for a long time or to surgical correction.

CONCLUSION

Higher number of patients undergoing lung transplantation, an increase in their life expectancy naturally lead to an increase in the number of bronchial complications diagnosed at different times after the operation. Observational bronchoscopy and interventional bronchology are an important part of a multidisciplinary approach to monitoring donor lung recipients. Timely diagnosis and operative, minimally invasive correction of bronchial complications allows avoiding the development of chronic dysfunction, reducing the quality and shortening the life expectancy of recipients after lung transplantation.

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